Allergic rhinitis

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Allergic rhinitis is a very common disorder that affects people of all ages, peaking in the teenage years. It is frequently ignored, underdiagnosed, misdiagnosed, and mistreated, which not only is detrimental to health but also has societal costs. Although allergic rhinitis is not a serious illness, it is clinically relevant because it underlies many complications, is a major risk factor for poor asthma control, and affects quality of life and productivity at work or school. Management of allergic rhinitis is best when directed by guidelines. A diagnostic trial of a pharmacotherapeutic agent could be started in people with clinically identified allergic rhinitis; however, to confirm the diagnosis, specific IgE reactivity needs to be recorded. Documented IgE reactivity has the added benefit of guiding implementation of environmental controls, which could substantially ameliorate symptoms of allergic rhinitis and might prevent development of asthma, especially in an occupational setting. Many classes of drug are available, effective, and safe. In meta-analyses, intranasal corticosteroids are superior to other treatments, have a good safety profile, and treat all symptoms of allergic rhinitis effectively. First-generation antihistamines are associated with sedation, psychomotor retardation, and reduced academic performance. Only immunotherapy with individually targeted allergens has the potential to alter the natural history of allergic rhinitis. Patients' education is a vital component of treatment. Even with the best pharmacotherapy, one in five affected individuals remains highly symptomatic, and further research is needed in this area.

Introduction

Allergic rhinitis is a prevalent yet underappreciated inflammatory disorder of nasal mucosa, which is characterised by pruritus, sneezing, rhinorrhoea, and nasal congestion.[1,2] It is mediated by early-phase and late-phase hypersensitivity responses—similar to those in allergic asthma—to indoor and outdoor environmental allergens.[3]

Although commonly regarded as merely a seasonal nuisance, allergic rhinitis can entail minimum persistent inflammation of mucosa,[4] which synergises with infective inflammation: thus, individuals with allergic rhinitis have additional difficulties with viral colds.[5] In children, the combination of rhinoviral infection, allergic sensitisation, and allergen exposure gives an odds ratio of 19 for admission to hospital for asthma.[6]

Findings of basic science and epidemiological studies show that allergic rhinitis is part of a systemic inflammatory process and is associated with other inflammatory disorders of mucous membranes,[1] including asthma, rhinosinusitis, and allergic conjunctivitis. An especially robust association is recorded with asthma, since most individuals with allergic and non-allergic asthma have rhinitis.[1] Poor asthma control is linked to moderate-to-severe rhinitis, which should be identified and treated.[1,7–9] A high prevalence of asthma is recorded in people with persistent and severe rhinitis.[10]

Allergic rhinitis adversely affects social life, school performance, and work productivity,[1] particularly in patients with severe disease.[11] Rhinitis symptoms have a detrimental effect on academic performance.[12] Akin to other functional domains, achievement at school is impaired further by use of suboptimum pharmacotherapy, notably antihistamines that cause sedation.[13] Loss of productivity, missed school and work days, and direct costs associated with treatment of allergic rhinitis create substantial costs to society. Severe financial losses per year in Sweden due to rhinitis have been reported.[14]

The ARIA (Allergic Rhinitis and its Impact on Asthma) guideline[1,15] focuses on quality of life as a principal consideration in assessment and treatment. It provides a global, evidence-based, pragmatic, stepwise approach to treatment of allergic rhinitis and has been updated and evaluated in recent years with GRADE (grading of recommendations assessment, development, and evaluation) methodology.[15] Avoidance of allergens is still a guiding principle, although this idea is typically difficult to implement. Intranasal corticosteroids are the one most effective class of drug because of anti-inflammatory effects on several different cell types, with some molecules showing no systemic bioavailability with long-term use, even in children. Immunotherapy is available via sublingual and subcutaneous routes at present, mainly for individuals with allergic rhinitis uncontrolled by pharmacotherapy and allergen avoidance. Immunotherapy is also the only treatment currently available that probably alters disease course, reducing progression not only of sensitisation but also of rhinitis to asthma.[16]

Epidemiology

Allergic rhinitis affects 400 million people worldwide, with high prevalence recorded in industrialised nations, especially English-speaking ones.[15] In the UK, seasonal allergic rhinitis was first noted by Bostock in 1819 and reported in further detail 4 years later.[17] The disorder was judged a rare affliction of wealthy people for at least the next century. However, a near quadrupling of primary-care consultations took place in the second half of the 20th century.[18] This increase in prevalence has been noted in all allergic diseases for reasons that have not been fully explained (see Cause). Researchers on the International Study of Asthma and Allergies in Childhood (ISAAC) project[19] investigated the prevalence and possible causes of atopic diseases, using standardised methods to describe the prevalence and severity of

asthma, rhinitis, and eczema with validated questionnaires in children around the world. ISAAC was divided into three phases: phase 1 allowed for comparisons of prevalence within and between countries; phase 2 provided a framework for aetiological research into genetic, lifestyle, environmental, and medical care variables; and phase 3 reassessed prevalence and severity measurements at least 5 years after initial responses were obtained.

The first phase of ISAAC took place between 1992 and 1998. Prevalence of rhinitis with itchy watery eyes within the past year was 0·8–14·9% (median 6·9%) in children aged 6–7 years and 1·4–39·7% (median 13·6%) in those aged 13–14 years. The lowest prevalence was in parts of eastern Europe and south and central Asia. The third phase of ISAAC (at least 5 years later) showed prevalence of rhinitis with itchy watery eyes in the past year was 1·8–24·2% in children aged 6–7 years (median 8·5%) and 1·0–45·0% (median 14·6%) in those aged 13–14 years. In the 6–7 years age-group, 67% of centres registered a substantial increase in prevalence, whereas 14% showed a decrease. In the 13–14 years age-group, 45% of centres had a substantial rise in prevalence, whereas 25% showed a fall. Wide variations in actual percentage changes for prevalence were seen across centres, ranging from –3·88% to 2·12% per year. The number of countries in which rhinitis is increasing exceeds those in which it is stable or decreasing, by contrast with asthma, for which prevalence seems to be stabilising or diminishing.[19]

About 80% of individuals diagnosed with allergic rhinitis develop symptoms before age 20 years.[20] In a German study,[21] complete follow-up data from 467 children (54% boys) were analysed. 12-month prevalence of allergic rhinitis quadrupled from 6% (at age 3 years) to 24% (at age 13 years) in children whose parents had no allergies and more than tripled from 13% (age 3 years) to 44% (age 13 years) in those who had at least one parent with an allergy. At least half the children with allergic rhinitis had severe persistent symptoms. Sensitisation to aero-allergens (adjusted odds ratio 18·9 [95% CI 9·3–38·4]) and having two parents with allergies (odds ratio 3·1 [1·1–9·3]) were significantly associated with allergic rhinitis.

Although boys are more likely than girls to have allergic rhinitis, this tendency reverses in puberty so that, by adulthood, men and women are affected equally.[1] Most individuals with allergic or non-allergic asthma have rhinitis.[22] Asthma and rhinitis frequently coexist in the same people throughout the world,[1,15] with asthma being most prevalent in those with persistent and severe rhinitis.[23] An association possibly exists between severity of asthma and rhinitis or rhinosinusitis.[24]

Cause

Atopy is the abnormal tendency to develop specific IgE in response to innocuous and ubiquitous environmental allergens.[20] Atopic diseases include allergic rhinoconjunctivitis, asthma, atopic dermatitis, and food allergies, and they tend to run in families. Atopy has been linked to many genetic loci on chromosomes 2, 5, 6, 7, 11, 13, 16, and 20.[20] Other risk factors for allergic rhinitis include ethnic origin other than white European, high socioeconomic status, environmental pollution, birth during a pollen season, no older siblings, late entry into nursery or preschool education (eg, at age 4 years and older), heavy maternal smoking during the first year of life, exposure to indoor allergens such as animal dander and dust mites, high concentrations in serum of IgE (>100 IU/mL before age 6 years), positive allergen skin-prick tests, and early introduction of foods or formula.[25] In adults, heavy alcohol consumption could be a risk factor as well.[26] Findings of several studies have shown that early environmental exposure to various infectious agents—such as hepatitis A, *Mycobacterium* spp, *Toxoplasma gondii*, the products of these agents (eg, endotoxins and lipopolysaccharides), or a combination of these—protects against development of atopy. This finding is consistent with principles of the hygiene hypothesis.[27]

	Agent
High-molecular-weight agents (IgE-mediated skin-prick and specific IgE tests possible)	
Laboratory workers	Laboratory animals
Swine confinement workers	Other animal-derived allergens
Laboratory workers and farm workers	Insects and mites
Grain elevator	Grain dust
Tobacco, tea, coffee, cacao, carpet, hot pepper, saffron, and dried fruit workers	Other plant allergens
Hospital and textile workers	Latex
Bakers	Flour, α amylase
Pharmaceutical and detergent industry	Biological enzymes
Fish industry and factory workers	Fish and seafood proteins
Low-molecular-weight agents (some evidence for IgE)	
Platinum refinery	Platinum salts
Epoxy resin production	Anhydrides
Reactive dyes, synthetic fibre, cotton, persulfate hairdressing, pulp and paper, shoe manufacturing	Chemicals
Low-molecular-weight agents (no or little evidence for IgE)	
Wood workers	Wood dust
Painters and urethane mould workers	Di-isocyanates
Health-care and pharmaceutical workers	Drugs

Tests for IgE are only relevant as shown when an IgE mechanism is implicated. Modified from reference 20, with permission of Mosby.

Table 1: **Triggering factors in occupational rhinitis**

Comorbidities

Allergic rhinitis is closely linked to other inflammatory diseases affecting respiratory mucous membranes, such as asthma, rhinosinusitis, and allergic conjunctivitis. Epidemiological evidence has repeatedly and consistently shown the co-existence of rhinitis and asthma.[1] Both allergic and non-allergic rhinitis are risk factors for

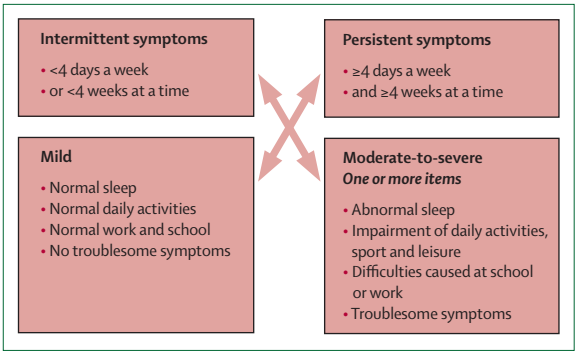

Figure 1: **ARIA classification of allergic rhinitis**[1]
Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy. Reprinted from reference 25, with permission of Wiley.

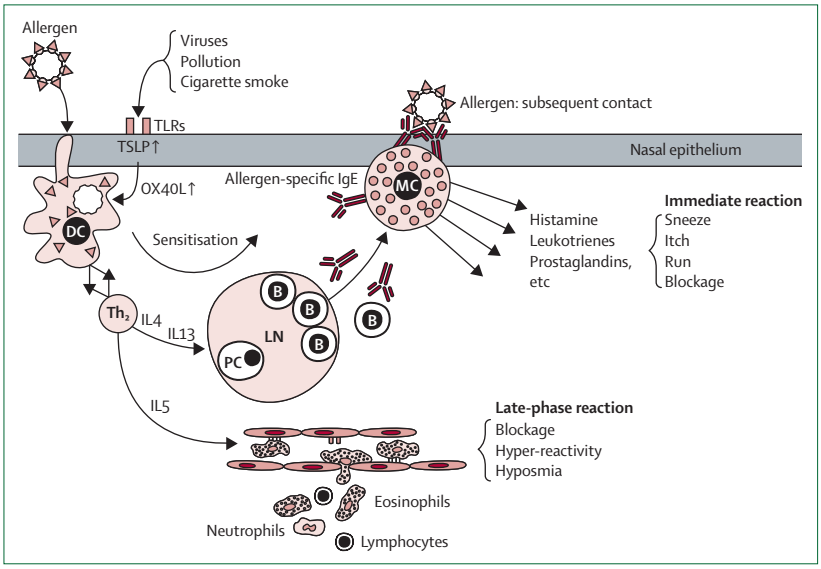

Figure 2: **Pathogenesis of allergic rhinitis**
TLRs=Toll-like receptors. TSLP=thymic stromal lymphopoietin. DC=dendritic cell. MC=mast cell. B=basophil. IL=interleukin. Th2=T helper 2 cell. LN=lymph node. PC=plasma cell. OX40L=OX40 ligand.

development of asthma,[28] with occupational factors (table 1) such as farming and woodworking giving high odds ratios also.[29] This association is important because early diagnosis and prevention by avoidance of these risks could be possible.

Evidence also exists to support a link between sinus disease and allergic rhinitis. 25–30% of individuals with acute sinusitis have allergic rhinitis, as do 40–67% of those with unilateral chronic sinusitis and up to 80% with chronic bilateral sinusitis.[30] Allergic rhinitis probably predisposes to sinusitis via nasal inflammation, resulting in nasal congestion and obstruction of sinus ostia. Decreased sinus ventilation leads to ciliary dysfunction, transudation of fluids, and stagnation of mucus, thereby promoting growth of bacterial pathogens.[30,31]

A link between rhinitis and otitis media with effusion has been proposed, with Eustachian tube dysfunction a suggested relevant factor.[32–34] However, no data from published controlled trials are available as yet to support this idea.

Allergic conjunctivitis is characterised by ocular itching, swelling, and discharge. Eye symptoms are present in 70% of people with seasonal allergic rhinitis and around 50% of those with perennial rhinitis.[35]

Quality of life

Until recent times, the focus on allergic rhinitis and its treatment revolved around symptoms and their improvement rather than on quality of life. Although allergic rhinitis causes bothersome practical drawbacks, we now understand that it could affect wellbeing in other ways.[15,35] Children can have difficulties at school because of learning impairment, secondary to distraction, fatigue, poor sleep, or irritability.[36] Children in the USA miss about 2 million school days a year because of allergic rhinitis. They might also be unable to take part in family or social events, resulting in emotional disturbances that manifest as anger, sadness, frustration, and withdrawal.[37] In the UK, performance in school examinations taken by children aged 15–16 years is worsened by allergic rhinitis, particularly if antihistamines that cause sedation are used.[12] With the short form 36 health survey—a generic questionnaire focusing on sleep, work, and school performance, family functioning, and social relationships—researchers noted that perennial allergic rhinitis impaired health-related quality of life as much as asthma did.[38]

Severe chronic upper-airway disease has been proposed to arise when rhinitis is not controlled by adequate pharmacotherapy.[39] This disorder could affect some 20% of people with rhinitis, with concomitant severe effects on quality of life and work and school ability.

Classification

Allergic rhinitis has been classified traditionally as seasonal or perennial, depending on sensitisation to cyclic pollens or year-round allergens such as dust mites, animal dander, cockroaches, and moulds. This scheme fails globally since seasons do not exist in many areas of the globe, and even where they do, many affected individuals have both seasonal and perennial allergen sensitisation.

The ARIA guidelines for classification and treatment of allergic rhinitis[1,15] have led to the definition of allergic nasal disease as intermittent or persistent and mild or moderate-to-severe (figure 1). This categorisation can be useful to establish pharmacotherapy. However, allergen-specific treatment needs to be incorporated with the seasonal and perennial classification to ascertain the correct allergen to be used in desensitisation.[30]

Figure 2 presents a schematic of the pathogenesis of allergic rhinitis. This disorder is initiated by an allergic immune response to inhaled allergens.[40] Atopic individuals have a genetic predisposition to become

sensitised to harmless allergens via activation of dendritic cells and T lymphocytes.[41] Dendritic cells are strategically located at mucosal surfaces to capture allergens and act as antigen-presenting cells, thereby presenting the allergenic peptide to T lymphocytes in draining lymph nodes. Observations suggest that the nature of the resulting response is driven by the milieu in which the dendritic cell is situated, with molecules such as thymic stromal lymphopoietin possibly promoting a T helper 2 (Th2) allergic response.[42–44] CD4+ T cells play a key part in initiation and orchestration of the allergic immune response through secretion of cytokines such as interleukins 4, 5, 10, and 13. Interleukin 4 is a cardinal cytokine in driving sensitisation to allergens by inducing the IgE class switch in B lymphocytes. IgE molecules are released into the bloodstream and bind to high-affinity receptors on the surface of tissue mast cells and circulating basophils. When allergens are deposited onto nasal mucosa of sensitised individuals, they bind allergen-specific IgE on the surface of mast cells, leading to rapid release of preformed mediators such as histamine, causing symptoms associated with the early nasal response—ie, sneezing, rhinorrhoea, and nasal itching. Both histamine and tumour necrosis factor α, and newly generated lipid mediators such as leukotriene C4 and prostaglandin D2, contribute to the influx of inflammatory cells—eg, eosinophils, CD4+ T lymphocytes, and basophils—by stimulation of expression of adhesion molecules on endothelial cells. Influx of these cells characterises the late allergic response, with nasal obstruction as the main presenting symptom. CD4+ lymphocytes represent the main source of interleukin 5. This cytokine has a key role in eosinophilic inflammation in allergic rhinitis through stimulation of eosinopoiesis, influx of eosinophils in mucosa, and eosinophil survival in tissue.

Allergen-specific IgE and eosinophilic nasal inflammation are typical features of allergic rhinitis, and these features distinguish allergic from other forms of the disorder. However, besides IgE production in bone marrow and lymph nodes, study findings show IgE production by B lymphocytes residing in nasal mucosa.[45] This localised IgE production is known as entopy, and it can arise in some individuals with non-allergic rhinitis with eosinophilia, in which nasal eosinophils are found without systemic evidence of allergen-specific IgE. Entopy could be missed by traditional allergen testing, which relies on the presence of allergen-specific IgE on cutaneous mast cells (for skin testing) or on circulating allergen-specific IgE (for serum testing, such as the radioallergosorbent [RAST] test). Unless allergen provocation tests are done, individuals with entopy might be classified falsely with non-allergic rhinitis or rhinopathy.[46] Free immunoglobulin light chains have been recorded in the serum and nasal secretions of some people with non-allergic rhinitis with eosinophilia, and this finding could be relevant to pathogenesis.[47]

The systemic nature of the allergic immune response has been recognised. One such example is upregulation of eosinophils in bronchial mucosa after nasal allergen challenge, and vice versa.[48,49]

Non-allergic neuronal mechanisms could have a role in the non-specific hyper-reactivity that is frequently seen in allergic rhinitis. Therefore, neurotrophins are prime candidates as mediators. These include nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and their receptors, pan-neurotrophin receptor p75 and tyrosine kinases A and B, which are expressed in nasal mucosa. In individuals with allergic rhinitis, exposure to nasal allergen leads to upregulation of BDNF and NGF expression. BDNF correlates positively with the maximum increase in total nasal symptom scores. BDNF and NGF exert immunomodulatory functions on eosinophils, which are capable of producing these factors.[50]

Regulatory T lymphocytes are important for maintenance of immune responses and T-cell homoeostasis. Naturally occurring CD4+CD25+ regulatory T cells, T regulatory 1 (Tr1) cells that produce interleukin 10, or both cell types suppress Th2 lymphocyte responses to allergens in health, whereas this inhibition is attenuated in allergic disorders.[51] Successful immunotherapy for Th2-mediated allergic conditions is associated with induction of Tr1 cells that produce interleukin 10 and transforming growth factor β.[52]

Diagnosis and differential diagnosis

Rhinitis is characterised clinically by one or more of the following symptoms: nasal itching, sneezing, nasal obstruction or congestion, rhinorrhoea (anterior or posterior), and sometimes, reduction of sense of smell (hyposmia). On exposure to allergen, symptoms of allergic rhinitis arise within minutes and can last for 1–2 h before improvement. Late-phase nasal symptoms can include nasal obstruction, hyposmia, postnasal mucous discharge, and nasal hyper-reactivity.[3] Allergic conjunctivitis is characterised by intense eye itching, hyperaemia, watering, and occasionally, periorbital oedema. It occurs in about 50–70% of people with allergic rhinitis.[35] Allergic conjunctivitis is the symptom that differentiates allergic rhinitis best from other forms of rhinitis, with an odds ratio of 2·85 (unpublished data). Conjunctivitis is related to both direct allergen contact with conjunctival mucosa and activation of nasal-ocular reflex.[53–55]

People with pollen-induced allergic rhinitis (particularly, birch pollen) could have an associated oral allergy syndrome. Typical immediate symptoms in such individuals include oral and pharyngeal hypersensitivity (itchiness, tingling, erythema, and angioedema of the tongue, lip, and soft palate) after oral contact with various fresh fruits and vegetables. This finding is consistent with the oral allergy syndrome.[56]

Rhinitis can be classified as allergic, non-allergic, and occupational and, thus, has many underlying causes.

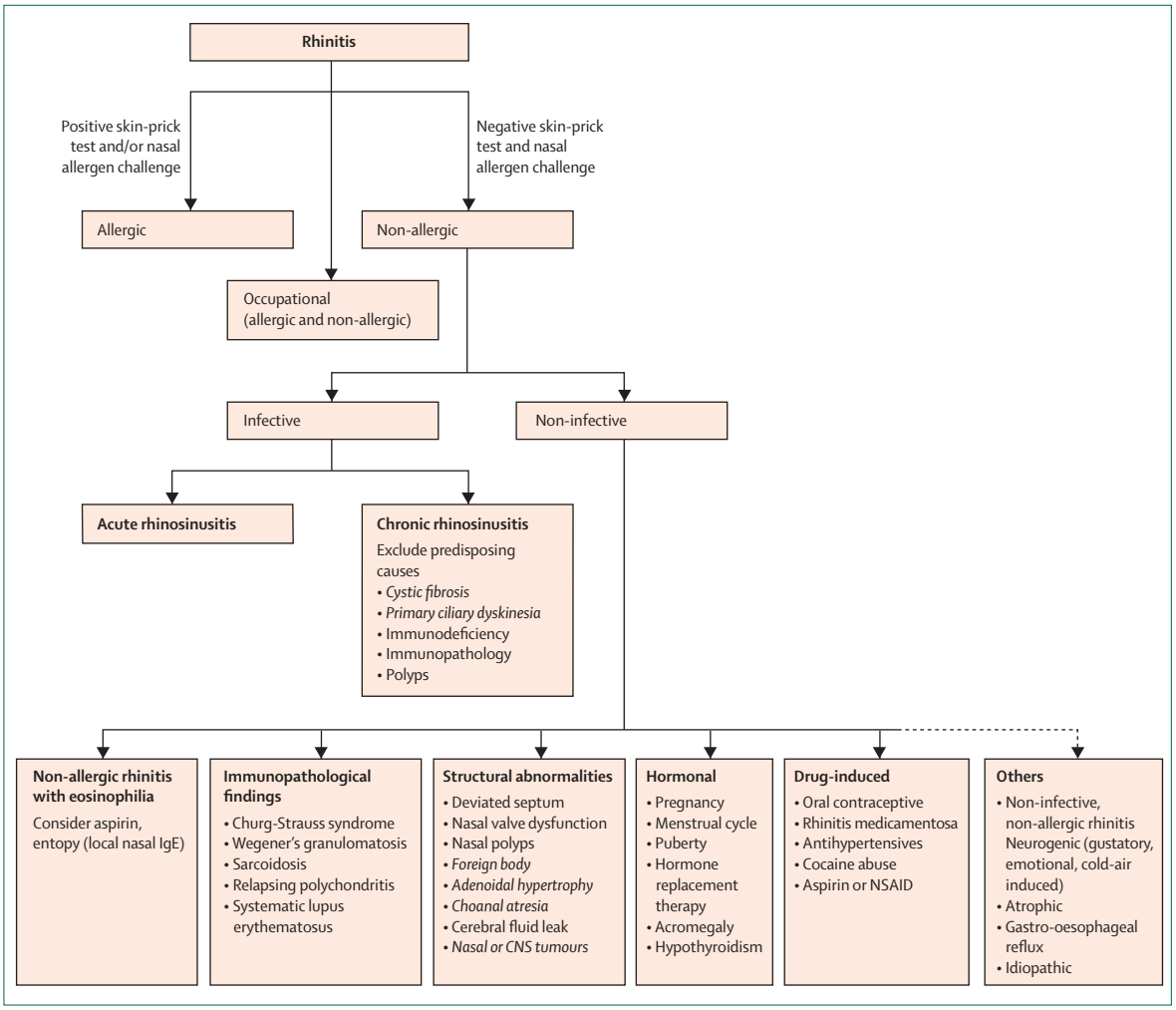

Figure 3: **Diagnostic algorithm for rhinitis**
Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID=non-steroidal anti-inflammatory drug.

About two-thirds of children and a third of adults with rhinitis will present with allergic rhinitis; the remainder have other forms, and some individuals cannot be classified (idiopathic rhinitis).[57] Although the definition of rhinitis is applied to diseases of the nasal passages, because of the anatomical relation with the paranasal sinuses, nasopharynx, middle ear, and lower airway, pan-airway involvement by the underlying disease process can happen and should be actively sought. As a result, rarely does rhinitis present as a single-organ disease entity, and an appropriate diagnosis can only be made if the upper airway is assessed in relation to associated structures. The link with the lower airway must always be considered. Importantly, a range of multisystem non-allergic diseases can mimic rhinitis (eg, Churg-Strauss syndrome, Wegener's granulomatosis, and sarcoidosis), although these disorders are much less common than allergic rhinitis.[57–60] A detailed comprehensive history—including questions about comorbidities—and thorough clinical examination are the two most important methods to aid accurate diagnosis, which is essential for delivery of targeted treatments. A patient's history can suggest allergenic triggers, reveal other allergic diseases, or provide a family history of allergy.

To confirm a diagnosis of allergic rhinitis, specific IgE reactivity to airborne allergens (relevant to the patient's history) needs to be recorded, via either skin-prick testing or by noting specific IgE in serum. This testing also provides information to direct environmental control measures or allergen-specific immunotherapy. Immediate hypersensitivity skin testing provides results within 15 min of doing the test, whereas results of RAST blood tests for specific IgE take several days to arrive, and the test can be less cost effective than skin-prick testing. However, RAST tests are useful in patients with dermographism, severe atopic dermatitis, or those unable or unwilling to temporarily stop antihistamine use. All IgE test results must be interpreted with

patient's history in mind, since both false-positive (sensitisation without clinical disease) and false-negative test results can arise.[61] Allergic rhinitis is triggered mainly by inhalant allergens, of which house dust mite and grass and tree pollens are the most usual, in most parts of the world.[62]

Non-allergic rhinitis encompasses a range of nasal pathological findings, and targeted investigation might be needed. Occupational rhinitis (table 1) includes a heterogeneous group of pathological findings (both via allergic and non-allergic mechanisms) that share a causal relation between work exposure and development of symptoms.[29,63]

The proposed diagnostic algorithm (figure 3) has been created by consideration of the most important points needed for assessment of rhinitis as well as the wide range of pathological findings manifesting with or mimicking the disorder. Differential diagnosis of rhinitis in children needs separate consideration.

Treatment

A successful therapeutic approach to allergic rhinitis should contain: patients' education, prevention of allergen or irritant contact, pharmacotherapy, and consideration of immunotherapy. Figure 4 presents an algorithm for treatment.

Patients' education

Patients should be educated about the nature of allergic disease, the likelihood of disease progression, and the need for treatment (which might have to be both regular and long term), in addition to addressing any concerns about safety of the treatment modalities used. Medical treatment aims to either reduce symptoms or alter the immune system to induce tolerance, or both of these. Information on the aims of treatment, probable benefits, and possible side-effects should be provided to prevent false expectations and enhance adherence to the prescribed regimen.

Patients should be informed about factors that aggravate nasal symptoms because avoidance of these could alleviate them. A suitable technique for nasal drug delivery must be shown to enable effective treatment and reduction of adverse events (webappendix p 1).

Allergen and irritant avoidance

Complete allergen avoidance stops symptoms of allergic rhinitis completely—for example, individuals who are allergic to pollen are asymptomatic at times when pollen is not prevalent. However, in trials of allergen reduction (eg, for house dust mite), complete avoidance has not been achieved and equivocal results or sparse benefits have been reported.[64] In a placebo-controlled study,[65] nasal filters (which prevent access of pollen to nasal mucosa) reduced rhinitis symptoms in people who were allergic to pollen.[65] Occupational rhinitis can sometimes be cured by early removal of the affected individual from the allergen or by implementation of adequate control measures.[29] This approach is important to prevent progression to occupational asthma.

Many patients with allergic rhinitis have nasal hyperreactivity to non-specific stimuli—eg, changes in temperature, air conditioning, pollution, and cigarette smoke. Thus, exposure to these stimuli should be

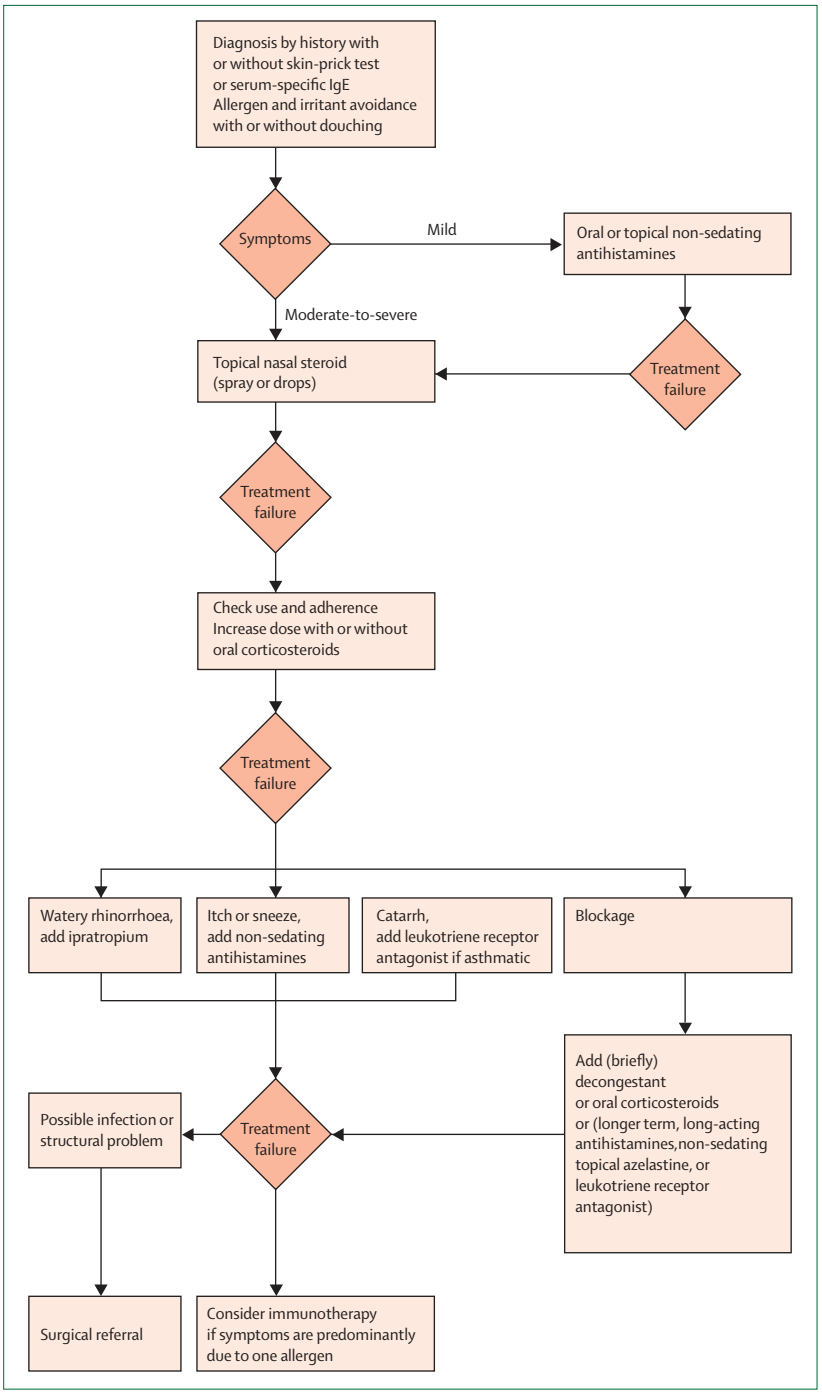

Figure 4: **Pharmacotherapy for rhinitis in adults and children**
Rhinorrhoea refers to clear discharge, predominantly anterior; catarrh refers to postnasal discharge. In the USA, immunotherapy is undertaken for many allergens. Reprinted from reference 25, with permission of Wiley.

See Online for webappendix

Panel: Advantages and disadvantages of pharmacotherapy for allergic rhinitis

Topical nasal treatments

Corticosteroids

- Sprays—fluticasone, mometasone, ciclesonide, triamcinolone, flunisolide, beclametasone
- Drops—fluticasone, betamethasone
- Advantages—most potent anti-inflammatory treatment; strong suppression of all nasal symptoms; effect on conjunctival symptoms; superior to other pharmacological treatments; clinically relevant improvement of quality of life; low bioavailability with recent molecules such as fluticasone
- Disadvantages—reduction of symptoms could take several days; incorrect use leads to treatment failure or adverse events such as epistaxis (in 10–15% of patients)

Antihistamines

- Azelastine, olopatadine
- Advantages—effective and safe treatment for nasal itch, sneezing, and rhinorrhoea; rapid onset of action (within 15 min)
- Disadvantages—neglect of systemic nature of allergic rhinitis; sparse effects on comorbid conditions (eg, conjunctival symptoms)

Chromones

- Sodium cromoglicate, nedocromil sodium
- Advantages—safe treatment with effect on nasal symptoms related to allergic rhinitis
- Disadvantages—several applications per day; weak effect on symptoms of allergic rhinitis

Anticholinergics

- Ipratropium bromide
- Advantages—good effect on rhinorrhoea only; nasal treatment with few adverse events
- Disadvantages—three applications per day; occasional reports of adverse events such as dry nose, epistaxis, urinary retention, and glaucoma

Decongestants

- Ephedrine, pseudoephedrine, xylometazoline
- Advantages—potent vasoconstrictive agents acting on nasal congestion only; rapid onset of action (within 10 min)
- Disadvantages—overuse by patients is common; development of rhinitis medicamentosa after prolonged use; occasional adverse events (eg, nasal irritation and increased rhinorrhoea)

Oral treatments

Antihistamines

- Second-generation antihistamines—levocetirizine and cetirizine, desloratadine and loratadine, fexofenadine, acrivastine, rupatadine, carebastine and ebastine
- First-generation antihistamines not recommended because of sedation and psychomotor retardation
- Advantages—effective for nasal symptoms of itch, sneezing, and rhinorrhoea; reduction of conjunctival, oral, and skin symptoms; rapid onset of action (within 1 h); few interactions with drugs or alcohol
- Disadvantages—regular treatment is more effective than on-demand therapy; modest effect on nasal congestion; sedation still happens in some patients

Corticosteroids

- Hydrocortisone, prednisolone
- Advantages—most potent rescue treatment, with beneficial effects for all symptoms, including nasal obstruction; systemic anti-inflammatory treatment
- Disadvantages—adverse events related to oral corticosteroid treatment; rarely indicated; only for short-term use

Antileukotrienes

- Leukotriene receptor antagonists (montelukast and zafirlukast) and leukotriene synthesis inhibitors (zileuton)
- Only montelukast is approved for allergic rhinitis in association with asthma in the UK
- Advantages—effective for nasal obstruction, rhinorrhoea, and conjunctival symptoms; effective for bronchial symptoms in patients with allergic rhinitis; generally well tolerated
- Disadvantages—not consistently effective; occasional reports of adverse events, such as headache, gastrointestinal symptoms, rash, and Churg-Strauss syndrome

Decongestants

- Pseudoephedrine
- Advantages—reduces nasal obstruction only available in combination with an antihistamine in some countries, but no better than antihistamine alone after a few days
- Disadvantages—frequent reports of side-effects, such as hypertension, insomnia, agitation, and tachycardia

avoided if possible. Saline douching, although most typically used in rhinosinusitis,[66] might also prove useful, allowing a reduction in the amount of pharmacotherapy needed to control symptoms in both children[67] and pregnant women.[68]

Pharmacotherapy

Despite the availability of guidelines for treatment, undertreatment of rhinitis is common.[2] In Europe, undertreatment of allergic rhinitis is attributable not only to underdiagnosis but also to prejudices of patients against some antiallergic treatments.[2] Guideline-directed management provides better control of symptoms and improved quality of life than does non-directed treatment.[69,70] The ARIA classification can be used to ascertain the best pharmacotherapy, which can be given topically or orally.[25]

The panel shows treatment modalities available and their major advantages and disadvantages. The two most effective treatments are intranasal corticosteroids and

immunotherapy, with corticosteroids less likely to cause harm (table 2).[71]

Intranasal corticosteroids are the most effective therapeutic agents for allergic rhinitis, as shown by the findings of three meta-analyses,[72–74] and they are superior or equal to the combination of an antihistamine and an antileukotriene.[75] Intranasal corticosteroids should be used for moderate-to-severe rhinitis, even in children, for whom good long-term safety data are available. In secondary care, 79% of adults with rhinitis showed a response to intranasal corticosteroids.[76] Rhinitis treatment, mainly with intranasal corticosteroids, has been shown to benefit people with asthma in criticised retrospective studies[77–79] and in one small prospective study.[80] Further randomised, double-blind, prospective studies are needed for confirmation. Van Cauwenberge and colleagues[81] reviewed all types of rhinitis treatment for their effects on asthma. Bronchial hyper-reactivity associated with allergen exposure in seasonal rhinitis[82] is reduced by nasal treatment with anti-inflammatory drugs.[83,84] Anti-IgE monoclonal antibodies are licensed for patients with severe asthma and could benefit those with associated allergic rhinitis.[85]

Two pharmacological treatments are not advised for people with allergic rhinitis. First, antihistamines that cause sedation worsen academic and work performance[13] and are associated with automobile and industrial accidents. Second, intramuscular corticosteroid injections are associated with potentially severe adverse events such as systemic side-effects and subcutaneous and muscular necrosis.[86]

	Benefit	NNT	Harm	NNH
Antihistamine				
Class mean	0·07	15·2	0·02	51
Nasal corticosteroid spray				
Class mean	0·23	4·4	0·02	48
Nasal antihistamines				
Azelastine (daily)	0·16	6·3	0·03	32
Azelastine (twice daily)	0·20	5·0	0·05	22
Other				
Montelukast	0·07	14·3	0·01	167
Omalizumab	0·08	12·3	0·08	13
Immunotherapy	0·22	4·6	0·07	14

Modified from reference 71, with permission of Current Science. NNT=number needed to treat to make one person better. NNH=number needed to harm to make one adverse event arise. A high number in the benefit section indicates a great benefit. A high number in the harm section indicates the most harm. The major adverse events were epistaxis for nasal steroids and sedation for antihistamines.

Table 2: **Benefits and harms of treatments for allergic rhinitis**

Immunotherapy

By contrast with symptom suppression by pharmacotherapy, immunotherapy aims to alter the immune system and could represent a cure for allergic rhinitis. Subcutaneous immunotherapy is effective in people with allergic rhinitis, with long-lasting reduction of symptoms and drug requirements, and it seems to prevent new sensitisations and asthma.[87,88] Prevention of asthma was noted in a cohort of children aged 6–14 years (n=205) with at least moderate rhinitis and eye symptoms—from grass or birch allergies—but no chronic asthma. Children were randomised to receive specific immunotherapy for 3 years or be in an open control group. Actively treated children had significantly fewer asthma symptoms after 3 years, as assessed by clinical diagnosis (odds ratio 2·52 [95% CI 1·3–5·1]). After a further 7 years, 147 individuals—now aged 16–25 years—were reassessed. Not only did substantial improvements in rhinoconjunctivitis and conjunctival sensitivity persist but also significantly fewer individuals who had received immunotherapy developed asthma, as assessed by clinical symptoms (odds ratio 2·5 [95% CI 1·1–5·9]). When adjusted for bronchial hyperresponsiveness and asthma status at baseline, and including all observations over the entire 10-year follow up (children with or without asthma at baseline, n=189; 511 observations), the odds ratio for no asthma was 4·6 (95% CI 1·5–13·7) in favour of subcutaneous immunotherapy.[16] 3–5-year treatment periods of this modality induce prolonged clinical remission accompanied by persistent alteration in immunological reactivity.[89]

Subcutaneous immunotherapy entails repeated injections with allergen extracts. It is reserved for people with severe allergic rhinitis whose symptoms are not controlled sufficiently with pharmacotherapy or who get side-effects from drugs that restrict treatment choices. Although subcutaneous allergen immunotherapy is effective, a small but definite risk of inducing a systemic allergic reaction is possible, which arises in less than 0·1% of those treated. Patients should only be given subcutaneous allergen immunotherapy in clinics supervised by doctors who are trained and skilled in adjustment of doses of immunotherapy. Because of the risk of severe systemic side-effects, patients need to be observed for 60 min after injection (30 min in the USA), and injections should only be undertaken in medical settings where resuscitation equipment and expertise are available.

Sublingual immunotherapy—for which only the initial dose needs medical supervision—is also effective in adults and children.[90,91] It seems to be safer than subcutaneous immunotherapy because side-effects are usually restricted to the upper airways and gastrointestinal tract; rare anaphylactic episodes, but no deaths, have been reported.[89] Evidence suggests that clinical and immunological benefits of sublingual immunotherapy persist after 3 years of continuous use,[91] similar to benefits noted with subcutaneous immunotherapy. Furthermore, local oral changes unique to sublingual immunotherapy are seen.[92] Although further studies on longevity and concordance, especially in children, are needed,[93] we are cautiously optimistic about sublingual

immunotherapy as an effective treatment and possible preventer of asthma.[94,95]

Surgery

Surgery is needed very rarely, except to improve the route for topical nasal treatment in patients with either turbinate hypertrophy or anatomical deformities, such as severe septal deviations or nasal-valve dysfunction that impairs nasal breathing. Endoscopic sinus surgery could be needed in people with chronic rhinosinusitis who are unresponsive to medical treatment.[1,30]

The future

Prevalence of allergic rhinitis continues to increase and will undoubtedly have substantial effects on the lives of many sufferers and society. Since 20% of people with rhinitis are not helped by guideline-directed pharmacotherapy, other treatments—such as allergen immunotherapy—obviously need to be more widely available, and new and more effective treatments should be sought.

Contributors

All authors contributed to writing of the report. GR and GKS produced some of the illustrations.

Conflicts of interest

GKS is a consultant or advisory board member for ALK, Abello, Britannia Pharmaceuticals, CMP Therapeutics, Groupo Uriach, GlaxoSmithKline, Merck, Sanofi-Aventis, Schering Plough, and UCB; received a grant from GlaxoSmithKline for a clinical trial; has received research funds from ALK, GlaxoSmithKline, UCB, and Schering Plough; has been a speaker for ALK, GlaxoSmithKline, Merck, Schering Plough, Uriach, and UCB; has co-written articles for Schering Plough and GlaxoSmithKline; receives royalties for the books *Fast Facts in Rhinitis*, *Investigative Rhinology*, and *Paediatric ENT*; received payment for development of a GlaxoSmithKline educational presentations video and a Schering Plough teaching slide set; and is a member of the ARIA and EPOS working groups. ANG has received grants from Alcon, Alexa, Allux, Amgen, Antigen Labs, Apotex, Astellas, AstraZeneca, Boehringer Ingelheim, Clay-Park Labs, Critical Therapeutics, Genentech, GlaxoSmithKline, Hoffmann-LaRoche, MAP, MEDA, Medicinova, MedPointe, Merck, Novartis, Nycomed (Altana), Pharmaxis, Rigel, Sanofi-Aventis, Schering-Plough, Teva, UCB, and Wyeth; and has been a speaker for MEDA, Sanofi-Aventis, and UCB. GR has had expenses reimbursed by ALK-Abello, Allergen Therapeutics, and UCB; and has received a fee for a lecture by Schering Plough. PWH has received grants from GlaxoSmithKline, MSD, and Schering Plough; and support from the Fund for Scientific Research (FWO) Flanders, and the Institute for Science and Technology (IWETE) Flanders.

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